REMARKS

The Office Action has rejected Claims 38, 40-46, 47, 54-56, 59, 60 and 63-66 under 35 U.S.C. §103 as defining subject matter which is allegedly rendered obvious by the teachings in U.S. Patent No. 6,340,475 to Shell et al. ("Shell et al.") in view of the teachings in WO 91/15548 to which Grillo et al. are inventors ("Grillo et al."). Further, Claims 38, 40-44, 46-48, 54-56, 59, 60 and 63-70 are rejected under 35 U.S.C. §103(a) as defining subject matter which is allegedly rendered obvious by the teachings in Shell et al. and Grillo et al. and further in view of the teachings in an article by Tobyn et al. in International Journal of Pharmaceuticals, 1998, 169, 183-194 ("Tobyn et al."). Further, Claims 38, 40-43, 46-48, 54-56, 59, 60 and 63-70 are rejected under 35 U.S.C. §103(a) as defining subject matter which is allegedly rendered obvious by the teachings in U.S. Patent No. 6,416,786 to Mulye et al. ("Mulye et al.") in view of the teachings in Grillo et al. In addition, Claims 38, 40-48, 54-56, 59, 60 and 63-70 are rejected under 35 U.S.C. §103(a) as defining subject matter which is allegedly rendered obvious by the teachings in Mulye et al. and Grillo et al. and further in view of the teachings in U.S. Patent No. 6,117,451 to Kumar ("Kumar"). Furthermore, Claims 38, 40-47, 54-56, 59, 60 and 63-66 are rejected under 35 U.S.C. § 103(a) as defining subject matter which is allegedly rendered obvious by the teachings in U.S. Patent No. 6,120,803 to Wong et al. ("Wong et al."). Moreover, Claims 38, 40-48, 54-56, 59, 60 and 63-70 are rejected under 35 U.S.C. §103(a) as defining subject matter which is allegedly rendered obvious by the teachings in Wong et al. in view of the teachings in Tobyn et al. Finally, Claims 38, 40-48, 54-56, 59, 60 and 63-70 are rejected under 35 U.S.C. §103(a) as defining subject matter which is allegedly rendered obvious by the teachings in Wong et al. in view of the teachings in Grillo et al.

Applicant has amended the claims, which when considered with the comments herein, are deemed to place the present case in condition for allowance. Favorable action is respectfully requested.

At the outset, Applicant wishes to thank Examiners Westerberg and Vu for the courtesy extended to Applicant's attorney during the telephone interview on April 7, 2009 and for their helpful suggestions. During the interview, Applicant's attorney discussed all of the issues raised in the Office Action with Examiners Westerberg and Vu. In particular, it was noted that all of the components recited in Claim 38 are within the core. This is in contrast with the teachings in the prior art cited, which disclose that the maltodextrin is in the coating and not the core. Examiners Westerberg and Vu agreed that this was an important distinction to make of record in the Response. In addition, even though it may be implicit in view of the teachings of the specification that these components are in the core, they recommended that the claims recite explicitly that the components recited in Claim 38 are present in the core.

In accordance with the interview, Applicant has amended Claims 38, 43, 44, 54, 55 and 56 by reciting that which is implicit from the teachings in the specification, namely, that the ingredients recited in Claim 38 are in the core. Support thereof is found in Paragraph 58, on Page 19 of the instant specification. Further, Applicant has corrected a typographical error in Claim 60.

In addition, Claims 71-73 have been added to the application. Support for the subject matter in these three claims is found in Paragraph 40 on Pages 12 and 13 of the instant specification.

Applicant respectfully submits that the amendment to Claim 38 does not narrow the scope of the claims, as Claim 38 recites what is implicit. Further, no new matter has been added to the application.

In support of the rejection of Claims 38, 40-47, 54-56, 59, 60 and 63-66, the Office Action cites Shell et al. in view of Grillo et al.

The present invention is directed to, inter alia, a sustained release pharmaceutical composition in oral dosage form comprising in the core thereof a mixture comprising a pharmaceutically effective amount of a drug, a sustained release carrier in an effective amount to retard the release of the drug from said composition when placed in an aqueous system, a water insoluble or partially water insoluble cellulose, maltodextrin and optionally a lubricating effective amount of a lubricant, wherein the weight ratio of cellulose to maltodextrin ranges from about 50:1 to 1:50. As described in the specification, the sustained release polymer influences the release of the drug from the formulation. However, this release can be fine tuned by the additional combination of maltodextrin and the water insoluble or partially water soluble cellulose, such as microcrystalline cellulose, silicified microcrystalline cellulose, and the like. As noted by Applicant in Paragraph 40 of the instant application, the presence of the excipient, the water insoluble or partially water soluble cellulose, had made it difficult to formulate controlled release tablets in the presence of a cellulose ether because they cause the disintegration of the tablet when in contact with an aqueous solution, causing the release of the medicament to be more rapid than desired. However, the inventor has found that this effect can be counteracted by the addition of maltodextrin. Thus, the present invention requires that the interaction of maltodextrin with the water insoluble or partially water soluble cellulose and the

interaction of both with the sustained release polymer and the drug. Thus, all four of these component need to be in the core so that they can interact directly.

If the maltodextrin were not present in the core, e.g., it could not interact with the water insoluble cellulose or partially water insoluble cellulose and counteract its effect in accelerating the release of the drug in the formulation. The cited prior art, in combination do not teach, disclose or suggest the presence of all four components in the core.

Shell et al. disclose oral dosage forms of drugs by incorporating them into polymeric matrixes comprised of hydrophilic polymers that swell upon imbibition of water to a size which is large enough to promote retention of the dosage form in the stomach during the feed mode. Examples of hydrophilic polymers include cellulose polymers and their derivatives, microcrystalline cellulose and xanthan gum. The Office Action refers to Example 4 of Shell et al. which discloses metformin controlled release dosage forms with various polymers such as xanthan gum, HPMC, hydroxyethyl cellulose and polyethylene oxide. Magnesium stearate may be included in the various formulations. The Office Action also refers to Example 10, which discloses a metformin dosage from comprising metformin, PEO, magnesium stearate and a coating comprised of HPMC.

However, as admitted in the Official Action, Shell et al. do not disclose the inclusion of maltodextrin in the pharmaceutical composition.

The Office Action alleges that it cites Grillo et al. for its alleged teaching of a composition containing maltodextrin. However, this is an oversimplification. Applicant respectfully submits that the teachings in Grillo et al. do not overcome the inadequacies of the primary reference. Grillo et al. disclose a method of coating substrates such as pharmaceutical

tablets with a protective film which comprises a mixture of a cellulosic polymer, maltodextrin and a plasticizer.

The combination of the references suggests, at most, the presence of maltodextrin in the coating of the pharmaceutical. The combination does not teach, disclose or suggest a matrix wherein the maltodextrin is mixed with, inter alia, the active ingredient, i.e. the drug, the water insoluble or partially water soluble cellulose and the sustained release polymer. Nor does the combination teach, disclose or suggest the presence of maltodextrin in the core of the pharmaceutical, as claimed.

It is respectfully submitted that the combination teaches away from the presence of maltodextrin in a sustained release pharmaceutical composition comprising cellulosic polymers such as HPMC, which is one of the sustained release polymers used in the present composition. As described in Grillo et al, on Page 14 thereof, the addition of maltodextrin to a cellulose polymer weakens the film strength, thereby making it easier to release the drug. This would tend to teach away from a sustained release formulation comprising a sustained release polymer and maltodextrin. However, in contrast, the inventor has found that maltodextrin in the presence of the drug, the sustained release polymer, such as cellulosic polymer and the water insoluble or partially water soluble cellulose tends to slow down the release. Therefore, the combination teaches away from adding maltodextrin to a sustained release polymer, such as cellulosic polymer, as claimed.

Thus, in conclusion, when the cited references are combined, the combination suggests a formulation in which maltodextrin is in the coating and not in the core. The presence of the drug, the sustained release polymer, the water insoluble or partially water soluble cellulose and maltodextrin in the core is not taught, disclosed or even suggested by the combination of the

primary and the secondary reference. Accordingly, the rejection is overcome, withdrawal thereof is respectfully requested.

In support of the rejection of Claims 38, 40-44, 46-48, 54-56, 59, 60 and 63-70 are rejected under 35 U.S.C. §103 the Office Action cites Shell et al. and Grillo et al. and Tobyn et al.

Applicant reiterates its comments with respect to Shell et al. and Grillo et al., the contents of which are incorporated herein by reference.

Tobyn et al. teach that there is no chemical or polymorphic difference between a sample of MCC and SMCC, indicating that the silicification process produces a material which is chemically and physically very similar to standard MCC.

Tobyn et al., do not overcome the deficiencies of the two references described hereinabove. As described hereinabove, the combination of Shell et al. and Grillo et al. suggest the presence of a maltodextrin in the coating – and not the core, as in the present application. Since Tobyn et al. merely disclose that there is no discernible chemical or polymorphic difference between silicified microcrystalline cellulose and standard grade microcrystalline cellulose, Tobyn et al. do not address the deficiency described hereinabove. Moreover, applicant respectfully submits that the combination of the three references suggests a composition wherein the maltodextrin is in the coating and not in the core. Furthermore, the combination does not teach, disclose or suggest maltodextrin interacting with the sustained release polymer, the drug and the water insoluble or partially water soluble cellulose. The combination does not teach, disclose or suggest a matrix where the active component, the water insoluble or partially water insoluble cellulose, maltodextrin and a sustained release carrier are

present in the core of the matrix, as presently claimed. Thus, Applicant respectfully submits that this rejection is overcome; withdrawal thereof is respectfully requested.

In support of the rejection of Claims 38, 40-43, 46-48, 54-56, 59, 60 and 63-70 under 35 U.S.C.§ 103(a), the Office Action cites Mulye et al. in view of Grillo et al.

Mulye et al. disclose a solid sustained release pharmaceutical tablet for administering to a host, comprising a therapeutically effective amount of a pharmaceutically active ingredient and a sustained release carrier, the sustained release carrier comprising (a) a hydrocolloid selected from the group consisting of xanthan gum, guar gum and alginic acid or a pharmaceutically acceptable salt thereof and (b) a cellulose ether, said hydrocolloid and cellulose ether being present in synergistic effective amounts to retard the release of the pharmaceutically active ingredient. The Office Action alleges that Mulye et al. disclose therein a filler such as microcrystalline cellulose, referring to Column 7, Lines 3-17 of Mulye et al. The Office Action admits that Mulye et al. do not disclose the use of maltodextrin in the formulation.

The Office Action cites Grillo et al, for allegedly teaching a method of coating substrates, such as pharmaceutical tablets comprising a mixture of cellulose polymers, maltodextrin and a plasticizer.

However, as with the earlier rejection, the combination does not teach, disclose or suggest a pharmaceutical composition wherein the maltodextrin is present in the core along with the drug, the sustained release polymer and the water insoluble or partially water insoluble cellulose.

As indicated hereinabove, in the discussions of Shell et al and Grillo et al., the combination of Mulye et al. and Grillo et al. suggests the presence of maltodextrin in the coating. The combination, even according to the Office Action, does not teach, disclose or suggest a

matrix wherein maltodextrin is mixed with, inter alia, the active ingredient, i.e., the drug, the cellulose or the sustained release polymer. Nor does the combination teach, disclose or suggest the presence of maltodextrin in the core of the pharmaceutical, along with these other components as recited in the claims of the present invention.

It is also interesting to note that none of the examples in Grillo et al. refer to a sustained release formulation. But interestingly, since Grillo et al., teach that the addition of maltodextrin to a drug formulation containing a cellulosic ether sustained release polymer tends to decrease the tensile strength, the combination teaches away from adding maltodextrin to a sustained release polymer, e.g., cellulosic ether. Thus, one of ordinary skill in the art would not combine any of the cellulose ether with maltodextrin.

Accordingly, for the reasons given hereinabove, this rejection is overcome, withdrawal thereof is respectfully requested.

Pursuant to the rejection of Claims 38, 40-48, 54-56, 59, 60 and 63-70 under 35 U.S.C. §103(a) the Office Action cites Mulye et al. and Grillo et al. as and Kumar et al.

The Office Action reiterates its comments regarding Mulye et al. and Grillo et al. It cites Kumar et al. for its teaching of metformin as an active ingredient.

Applicant reiterates the comments hereinabove, regarding the combination of Mulye et al. and Grillo et al., the contents of which are incorporated herein by reference. As described hereinabove, the combination do not teach, disclose or suggest a sustained release formulation in which the maltodextrin is present in the core of the pharmaceutical composition along with the drug, the sustained release polymer and the water insoluble or partially water soluble cellulose.

Kumar et al. do not overcome this deficiency. Kumar discloses a metformin HCl formulation having the following composition:

(a) 70-79% by weight metformin,

(b) 10-20% by weight HPMC, having a MW of 80,000-90,000, a particle size range of about 400 to 600 microns and a density range of 0.25 to 0.70 g/ml,

(c) to 15% by weight of hydroxypropyl cellulose having a number average MW of 300,000 to 1,000,000,

(d) 1-10% by weight of dibasic calcium phosphate,

(e) 1-10% by weight of microcrystalline cellulose,

(f) 5 to 15% by weight povidone,

(g) 0.1 to 2% by weight colloidal silicon dioxide,

(h) 0.1 to 2% by weight of a lubricant.

Thus, Kumar et al. do not overcome the deficiency of Mulye et al. and Grillo et al. The combination would suggest maltodextrin in the coating, and not in the core. More specifically, the teaching would not suggest the presence of a drug with the sustained release polymer such as cellulosic ether, and the water insoluble or partially water soluble cellulose ether, and hydroxypropylmethyl cellulose in a sustained release pharmaceutical composition, as claimed. Therefore, for the reasons provided herein, it is respectfully submitted that this rejection is overcome. Withdrawal thereof is respectfully requested.

Pursuant to another rejection under 35 U.S.C. §103 of Claims 38, 40-47, 54-56, 59, 60 and 63, the Office Action cites Wong et al.

According to the Office Action, Wong et al. disclose a dosage form adopted for retention in the stomach that is used for sustained delivery of an active agent. In one embodiment, according to the Office Action, Wong et al. disclose a composition comprising an active ingredient, a polymer matrix which is a mixture of high molecular weight, water-soluble

polymers and a hydroattractant, such as a water insoluble polymer, an optional non-polymer water soluble excipient and a band of insoluble material. According to the Office Action, the polymer can be a single polymer or a mixture. It lists examples of water-soluble polymers which include HPMC, xanthan gum and maltodextrin, referring to Column 5, Lines 55 et seq. An example of a hydroattractant includes microcrystalline cellulose, low-substituted hydroxypropyl cellulose, among others (See Column 6, Lines 3-5). However, it lists various sustained release polymers; Wong et al. disclose that the core may contain one of the listed polymers or a blend of the polymers. But, it does not identify the various blends, i.e., it does not teach or disclose that maltodextrin can be present in the core with other hydrophilic polymers. The Office Action concurs. As admitted by the Office Action, Wong et al. do not explicitly disclose a sustained release composition containing maltodextrin, as recited in Claim 38. Moreover, it appears that there is no specific teaching or suggestion in Wong et al. that combines maltodextrin with a sustained release polymer. Wong et al. do not specifically teach a mixture of maltodextrin and a sustained release polymer.

Therefore, Wong et al. disclose that the matrix therein has a band of insoluble material, such as maltodextrin circumscribing a portion of the outer surface of the polymer matrix. In other words, the maltodextrin is not in the core, but circumscribes a portion of the outer surface of the polymer matrix. Thus, Wong et al. do not teach, disclose or suggest the present formulation in which maltodextrin along with the sustained release polymer, the water insoluble cellulose or the partial water insoluble cellulose is in the core, as claimed.

Furthermore, Applicant directs the attention of the United States Patent and Trademark Office to the exemplification in the specification. In particular, attention is directed to Example 8 which compares the release profile of two respective formulations of the present invention

wherein the core contains a representative drug, metformin, a cellulose containing a sustained release polymer, HPMC and xanthan gum, and a representative excipient, silicified microcrystalline cellulose and maltodextrin are present in the core, and the ratio of silicified microcrystalline cellulose to maltodextrin is 1:1 and 9:1, respectively, and compared with Comparative Example 2, which does not contain maltodextrin - - let alone maltodextrin in the core. See also Figure 2. As shown by the above data, and Figure 2 which show the release profile of the drug in the formulation, the absence of maltodextrin increases the rate of the release of the metformin (top line). However, when the core contains metformin as the drug, the sustained release polymers, HPMC and xanthan gum, silicified microcrystalline cellulose and maltodextrin, the release rate was slower. This shows that when the core contains the hyphorphillic sustained release polymer, the drug and the water insoluble cellulose in the absence of maltodextrin, the release profile is faster than when the core additionally contains maltodextrin in the prescribed range.

Accordingly, for these reasons, this rejection is overcome; withdrawal thereof is respectfully requested.

Pursuant to the rejection of Claims 38, 40-48, 54-56, 59, 60 and 63-7 under 35 U.S.C. §103(a), the Office Action cites Wong et al. and Tobyn et al.

Applicant reiterates its comments regarding Wong et al., the contents of which are incorporated herein by reference.

Tobyn et al. do not overcome the inadequacies of Wong et al. It is cited for the alleged substitution or equivalence of SMCC for microcrystalline cellulose.

The arguments presented hereinabove regarding Wong et al. are applicable. Tobyn et al. do not address the inadequacies of Wong et al. It merely discloses that there is no discernable

chemical or polymorphic difference between microcrystalline cellulose and silicified microcrystalline cellulose. Thus, Tobyn et al. do not address the deficiency of Wong et al. described hereinabove. Thus, the combination of Wong et al. and Tobyn et al. do not teach, disclose or suggest a sustained release formulation wherein the drug, the sustained release hydrophilic polymer, maltodextrin and the water insoluble or partially water soluble cellulose are all present in the core, as claimed.

Accordingly, for the reasons provided this rejection is overcome; withdrawal thereof is respectfully requested.

Pursuant to the rejection of Claims 38, 40-48, 54-56, 59, 60 and 65-70 under 35 U.S.C. §103(a), the Office Action cites Wong et al. further in view of Grillo et al.

Applicant reiterates the comments hereinabove with respect to Wong et al.

As described hereinabove Grillo et al. is cited for the teaching of the combination of maltodextrin with cellulose polymers in the coating.

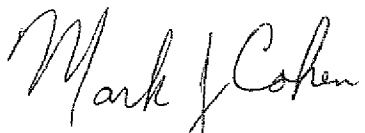
Applicant respectfully submit that the our comments hereinabove with respect to Shell et al. and Grillo et al. and Mulye et al. with Grillo et al, are applicable here. More specifically, the combination of Wong et al. and Grillo et al. suggest the presence of maltodextrin in the coating, and not the core, as claimed. Further the combination would not suggest a sustained release formulation wherein the drug, the sustained release polymer, the water insoluble or partially soluble cellulose and the maltodextrin are in the core.

In addition, Grillo et al. suggest that the addition of maltodextrin to cellulose polymer weakens the strength of the coat, thereby making it easier for the coating to be broken. Thus, the combination of Wong et al. and Grillo et al. would tend to teach away from a sustained release polymer containing a sustained release polymer, e.g., a cellulosic ether, the drug, the water

insoluble or partially water soluble drug and maltodextrin, as claimed. Thus, for the reasons provided, this rejection is overcome; withdrawal thereof is respectfully requested.

Thus, in view of the Amendment to the Claims and the Remarks it is respectfully submitted that the present case is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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